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Patterns of progression in a contemporary cohort of 447 patients with smoldering multiple myeloma

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Dear editor,

Smoldering multiple myeloma (SMM) is considered an asymptomatic plasma cell disorder preceding multiple myeloma (MM). The course of SMM disease is heterogenous, largely driven by disease biology and tumor burden [1, 2]. Routine clinical surveillance or early treatment, mostly within clinical trials, is thus based on the likelihood of developing a myeloma defining event (MDE) requiring systemic treatment [3]. Current stratification models for risk of progression include bone marrow plasma cell (BMPC) infiltration, monoclonal (M) protein component, ratio of involved/uninvolved serum free light chains (FLCr), and cytogenetic abnormalities [4, 5]. Early systemic treatment of high-risk SMM has shown to improve progression free survival in two trials and overall survival (OS) in one of them [6, 7]. However, early treatment of SMM is not considered a standard of care [8, 9].

The revision of the diagnostic criteria for MM and its precursor states in 2014 ushered a novel era in the treatment of MM with MDE encompassing biomarkers of malignancy besides established criteria for end-organ damage [10]. The inclusion of biomarkers of malignancies into MDE allows treatment of MM before end-organ damage can occur. In patients diagnosed SMM, end-organ damage can thus potentially be prevented.

In their current publication, N.H. Abdallah and colleagues from the MAYO Clinic (Rochester, MN, USA) retrospectively investigated the mode of progression in 406 patients with SMM [11]. They demonstrate that among MDE, bone lesions and anemia (e.g., 36% and 34% in patients with untreated high-risk SMM) remain the prevailing criteria of end-organ damage. Among patients untreated for high-risk SMM, only 13 patients (26%) progressed only by biomarkers of MM malignancy and 23 patients (45%) by clinically significant MDE (hypercalcemia, renal insufficiency, or bone lesions). These important observations pose a spotlight on the current debate on whether and how to observe or treat SMM in the current era.

In the present analysis, we aimed to validate the observations from the previous report and further dissect the patterns of progression in patients with SMM.

This retrospective study included 447 patients diagnosed with SMM between February 13, 2009, and July 28, 2023, at the Heidelberg University Hospital (Heidelberg, Germany). SMM was defined according to the current 2014 International Myeloma Working Group (IMWG) criteria [10]. Recommended follow-up for patients with SMM at our institution comprised routine assessments every 3 months and yearly whole-body magnetic resonance imaging (MRI) scans in all patients for the first 5 years from initial diagnosis in accordance with the current IMWG imaging recommendations [12]. Bone marrow diagnostics or whole-body low-dose CT scans were performed only in case of dynamic M protein/FLCr, symptoms, or suspected progression. The study was approved by the institutional ethics committee (S-599/2022 and S-578/2023, Medical Faculty, Heidelberg University, Heidelberg, Germany) and all patients provided written informed consent.

SMM patients were stratified using the validated 2018 MAYO risk score [4, 13]. Based on the score, patients were categorized into high (≥2 points), intermediate (1 point), or low risk (0 points) [13]. Analyzed MDEs were defined in accordance with the 2014 IMWG criteria [10]. Biomarkers of malignancy (denoted with the acronym SLiM) include BMPC ≥ 60%, FLCr≥100, and more than 1 focal lesion (>5 mm) on MRI. End-organ damage (denoted with the acronym CRAB) is defined as hypercalcemia (>2.75 mmol/L), renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >177 µmol/L), anemia (hemoglobin <100 g/L or >20 g/L below the lower limit of normal), and bone lesions (one or more osteolytic lesions on skeletal radiography, CT, or PET-CT). Time to progression (TTP) was defined as time from SMM diagnosis to time of either last contact, censoring (e.g., for treatment of SMM) or MM diagnosis, whichever occurred first. Start of systemic therapy of SMM and death without prior progression to MM were treated as competing events. Cumulative incidence of risk of progression was estimated with the Aalen-Johansen estimator. Analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA, version 2108) and R (Vienna, Austria, version 4.3.2, www.r-project.org).

The baseline characteristics of the 447 patients are described in Supplemental Table 1. Median age at SMM diagnosis was 60 years (range 29–93) and 44% were female. At least one whole-body MRI during observation and prior to progression or censoring was performed in 382 of 447 patients (85%). MAYO 2018 risk score was high in 82 patients (22%), intermediate in 120 patients (32%), low in 177 patients (47%) and unknown in 68 patients. With a median follow-up of 5.8 years (IQR 3.2–8.1), 140 patients (31%) progressed to MM requiring treatment and 44 patients (10%) had died. The median TTP of the entire cohort was 13.1 years (95% CI 3.3–not estimable [NE]). With respect to the MAYO2018 score, median TTP was 2.6 years (95% CI 1.0–9.9), 11.6 years (95% CI 4.7-NE), NE years (95% CI 8.3-NE) and 6.9 years (95% CI 2.0-NE) in the high, intermediate, low risk group and patients with unknown risk status, respectively.

One-hundred-and-twenty-nine patients (92%) progressed with at least one MDE whereas 11 patients (8%) progressed due to non-MDEs requiring treatment. Among these 11 patients, 5 patients had developed AL amyloidosis, two patients had high and dynamic M protein-/FLC-values, one patient had monoclonal gammopathy of renal significance, one patient had cutaneous manifestations of monoclonal gammopathy, one patient had primary plasma cell leukemia, and one patient had b symptoms likely related to SMM.

Figure 1 displays the frequency of MDEs across MAYO2018 risk groups and overall cohort. In the high-risk group, the most common MDEs were FLCr ≥ 100, bone lesions, anemia, and more

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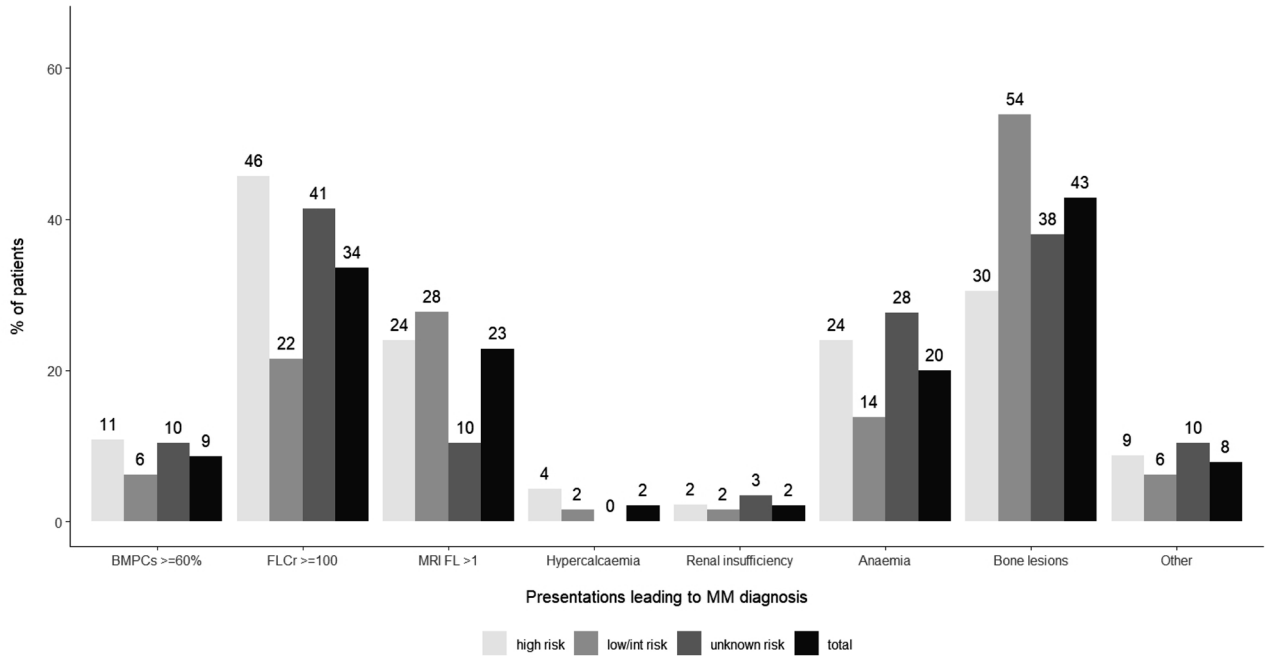

Fig. 1 MDEs in patients with smoldering multiple myeloma according to high, low/intermediate or unknown risk status. MDE myeloma defining event, MM multiple myeloma, BMPCs bone marrow plasma cells, FLCr free light chain ratio, MRI magnetic resonance imaging, FL focal lesion.

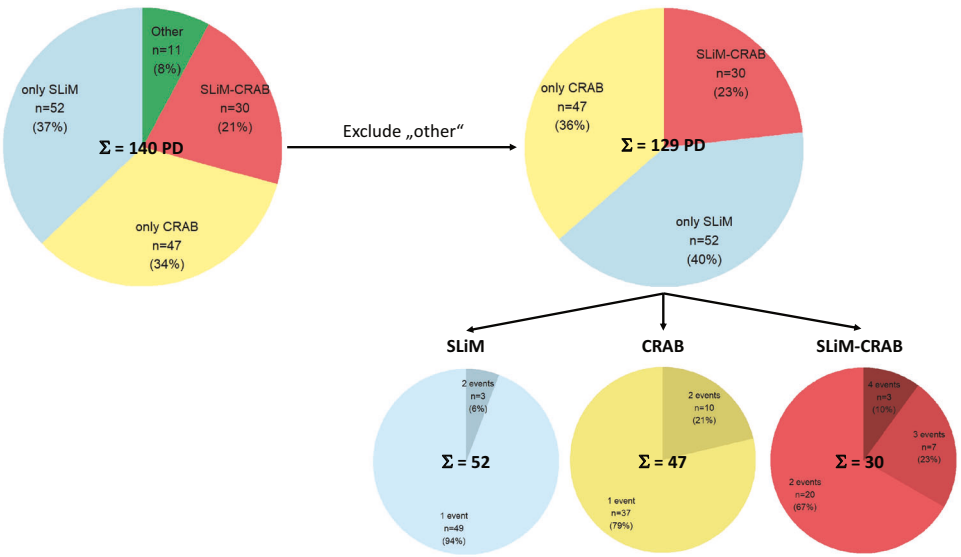

Fig. 2 Distribution of MDE among patients with smoldering multiple myeloma according to SLiM-CRAB criteria. MDE myeloma defining event, S: ≥60% bone marrow plasma cells (BMPCs); Li: free light chain ration ≥100; M: >1 MRI-defined focal lesion, C hypercalcemia, R renal insufficiency, A anemia; B bone lesions.

than one focal lesion on MRI in 21/46 (46%), 14/46 (30%), 11/46 (24%), and 11/46 (24%) patients, respectively. In the intermediate/low risk groups, bone lesions, anemia, FLCr ≥ 100, and more than one focal lesion on MRI in 35/65 (54%), 9/65 (14%), 14/65 (22%), and 18/65 (28%) patients were the most frequent MDEs. In the overall patient cohort of patients with progression, bone lesions, FLCr≥100, more than one focal lesion on MRI and anemia were most common in 60/140 (43%), 47/140 (34%), 32/140 (23%), and 28/140 (20%) patients, respectively. 66/140 (47%) patients in the overall cohort of patients with progression had clinically significant MDEs.

Among 129 patients progressing with at least one MDE, 86 (67%) had one MDE, with 49 (38%) patients having one SLiM, and 37 (29%) patients having one CRAB criterion (Fig. 2). Among patients with FLCr≥100 as sole MDE, 16 vs. 15 patients had a 24-h urine light chain excretion <200 mg/d vs. ≥200 mg/d. 43 patients had more than one MDE with 3 (7%) patients having SLiM-only features, 10 (23%) patients having CRAB-only features, and 30 (70%) patients having SLiM-CRAB features. When further dissecting patterns of progression, 52/129 (40%), 47/129 (36%) and 30/129 (23%) patients progressed with SLiM only, CRAB only or SLiM-CRAB criteria. Among patients with SLiM only criteria, 49/52 (94%) had one and 3/52 (6%) had two SLiM criteria. In patients with CRAB only features, 37/47 (79%) had one feature, 10/47 (21%) had two features and no patient had three or four features. SLiM-CRAB-positive patients presented with either two (20/30, 67%), three (7/30, 23%), or four (3/30, 10%) features. In

patients with at least one SLiM criterion, 30/82 (37%) presented with additional CRAB criteria, whereas in patients with at least one CRAB criterion, 47/77 (61%) presented without additional SLiM criteria.

Our results are in line with the results reported by Abdallah and colleagues. Both size of the overall cohort (406 and 447 patients) and progression events (159 and 140 patients) as well as baseline characteristics are comparable [11].

In both the MAYO Clinic and Heidelberg University Hospital patient cohorts, most patients present with bone lesions as MDE, followed by anemia and BMPCs/FLCs criteria in the MAYO Clinic cohort, followed by FLCr and MRI criteria and then anemia in the Heidelberg cohort. In the MAYO Clinic cohort, marrow lesions on MRI are detected in <5% of progression events, whereas they are detected in >20% of progression events in the Heidelberg University Hospital cohort. This discrepancy may originate from the high number of routine MRIs offered to SMM patients during the course of surveillance at our institution. Thus, MRI is an important tool for the early detection of bone lesions, especially in patients with high-risk SMM as currently investigated in the diagnostic study SPOTLIGHT (NCT06212323). Whether additional diagnostics, such as repeated bone marrow examinations, can further improve early identification of patients with progressive SMM needs to be evaluated.

A considerable number of SMM patients (52/129, 40%) who progress into MM requiring therapy solely present with biomarkers of MM malignancy and without end-organ damage. Equally, 30/82 (37%) of SLiM-positive patients have accompanying CRAB criteria. While this can be considered a substantial improvement in preventing end-organ damage, overtreatment remains a potential risk in SMM patients. Further studies are needed to describe the actual number of patients with SMM solely progressing with biomarkers of malignancy and to define the optimal timepoint to initiate treatment prior to developing end-organ damage. This is particularly important in patients with FLCr≥100 as sole MDE [14, 15], and FLCr≥100 should prompt repeated reassessment, measurement of 24-h urine light chain excretion and search for other MDE criteria. In case of a 24-h urine light chain excretion ≥200 mg/d, a high risk of progression and potential renal damage should be suspected [15]. In contrast, SMM patients with a 24-h urine light chain excretion <200 mg/d have shown a similar risk of progression whether their FLCr was ≥100 or <100 [15].

In conclusion, our results from the Heidelberg University Hospital cohort of SMM patients support the findings of Abdallah et al. very well and underline that although many progressive patients can already be identified while presenting only biomarkers indicative of progressive MM, there is still the need for further diagnostic improvement to identify more progressive patients before they present with end-organ damage. More frequent MRI diagnostics, especially in high-risk patients, promise to be a useful tool for this purpose.

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AUTHOR CONTRIBUTIONS

The conception and design of this study were done by AW, MH, TH, and EKM. MSR, CMT, HG, and EKM provided study material and patients. AW, MH, TH, KZ, SKS, and EKM contributed to data collection and assembly. Administrative support was given by MSR, CMT, HG, and EKM. AW, MH, TH, AV, and EKM analyzed and interpreted the data. First draft of the manuscript was written by MH and EKM. Interpretation and discussion of results, manuscript editing, further writing and final approval of the manuscript was done by all authors.

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COMPETING INTERESTS

EKM reports consulting or advisory role with Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline, and Takeda; honoraria from Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline, and Takeda; research funding from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, and Takeda; and travel accommodations and expenses from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, Stemline, and Takeda. AV reports consulting and honoraria

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ADDITIONAL INFORMATION

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